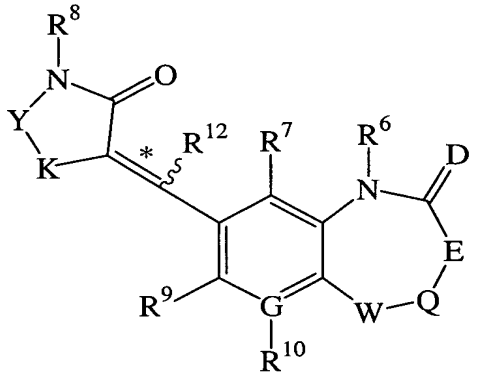
CLAIMS

What is claimed is:

1. A compound of Formula I:



I

or a pharmaceutically acceptable salt thereof;

wherein W is selected from the group consisting of: O, S, and NR^{21};

wherein R^{21} is selected from the group consisting of: -H, $-CH_3$, a C_{1-6}alkyl, and phenyl;

wherein Q is $(CR^2R^3)_n$,

wherein R^2 and R^3 are independently selected from H or $-CH_3$,

wherein n is 0 or 1;

wherein E is $(CR^4R^5)_p$,

wherein R^4 and R^5 are independently selected from H or $-CH_3$,

wherein p is 0 or 1;

wherein D is O or S;

wherein R^6 is selected from the group consisting of H, a C_{1-9}alkyl, a –C(O)-C_{1-9}alkyl, a C_{3-8}cycloalkyl, a -C(O)-C_{1-3}alkylene-C_{3-8}cycloalkyl, a (C_{1-6}alkyl)-C_{3-8}cycloalkyl, a -O-CH_2-C_{3-8}cycloalkyl, a group of formula -A-B-L, and a group of formula -X-V-U-T,

wherein A is absent, or -O-,

wherein B is a C_{1-6}alkylene,

wherein L is $-OR^{24}$, $-C(O)R^{24}$, $-OC(O)R^{24}$, $-C(O)OR^{24}$, $-SO_2-R^{24}$, $-NHC(O)R^{24}$, $-NR^{24}R^{26}$, $-C(O)-NR^{24}R^{26}$, $-OC(O)NR^{24}R^{26}$, $-NC(O)OR^{24}$, a 3- to 8-membered heterocycloalkyl, a 6- to 11-membered bicyclic heterocycloalkyl, a 6- to 9-membered bridged bicyclic heterocycloalkyl, a 5-membered heteroaryl, a 6-membered heteroaryl, an 8-to 12-membered bicyclic heteroaryl, a phenyl, a naphthalenyl or a 9- to 12-membered bicyclic aryl;

wherein R^{24} and R^{26} are independently selected from the group consisting of: a C_{1-6}alkyl, phenyl, naphthalenyl or a 9- to 12-membered bicyclic aryl, a 5-membered heteroaryl, a 6-membered heteroaryl, an 8-to 12-membered bicyclic heteroaryl, a C_{1-6}alkylene-phenyl, C_{1-6}alkylene-naphthalenyl or a C_{1-6}alkylene-(9- to 12-membered bicyclic aryl), a C_{1-6}alkylene(5-membered heteroaryl), C_{1-6}alkylene(6-membered heteroaryl), a C_{1-6}alkylene(8- to 12-membered bicyclic heteroaryl), C_{1-6}alkylene-(3- to 8-membered heterocycloalkyl), C_{1-6}alkylene-(6- to 11-membered bicyclic heterocycloalkyl), C_{1-6}alkylene-(6- to 9-membered bridged bicyclic heterocycloalkyl), and H;

wherein X is C_{1-3} alkylene,–O-C_{1-3} alkylene, -C_{1-3}alkylene-CO-, -C_{1-3} alkylene-C(O)O-, -C_{1-3}alkylene-C(O)-CH_2-, -C_1-C_3 alkylene-O-,

$-C_{1-3}$ alkylene-S(O)-, $-C_{1-3}$ alkylene-S-, or $-C_{1-3}$ alkylene-SO_2-;

wherein V is a 9- to 12-membered bicyclic arylene, a naphthalenylene, a phenylene, a 5-membered heteroarylene, a 6-membered heteroarylene, an 8- to 12-membered bicyclic heteroarylene, a 3- to 8-membered heterocycloalkylene, a 6- to 11-membered bicyclic heterocycloalkylene, or a 6- to 9-membered bridged bicyclic heterocycloalkylene;

wherein U is -CO-, -O-, $-CH_2-O-$, a C_{1-3} alkenylene, $-(CH_2)_m-$, $-O-CH_2-$, NH-, or is absent, wherein m is an integer from 1 to 3;

wherein T is a C_{3-8}cycloalkyl, a 9- to 12-membered bicyclic aryl, a naphthalenyl, a phenyl, a 5-membered heteroarylene, a 6-membered heteroarylene, an 8- to 12-membered bicyclic heteroarylene, a piperizinyl, a pyridinyl, a 3- to 8-membered heterocycloalkyl, a 6- to 11-membered bicyclic heterocycloalkyl, a 6- to 9-membered bridged bicyclic heterocycloalkyl, a piperidinyl, a morpholinyl, or an aza-spiro[5.5]undecyl;

wherein R^7 is H, F, CF_3, or CH_3;

wherein R^8 is H, $-CH_2COOH$, phenyl, $-CH_3$, a C_{1-6}alkyl, or a C_{2-6}alkenyl;

wherein Y is C(O), or C(S);

wherein K is NH, O, CH_2, or S;

wherein G is N or C;

wherein R^9 is H, F, CF_3, or CH_3;

wherein R^{10} is H, -O-C_{1-3}alkyl, a C_{1-3}alkyl, NO_2, $NR^{16}R^{18}$, a S-C_{1-3}alkyl, F or Cl,

wherein if G is N, then R^{10} is absent,

wherein R^{16} and R^{18} are independently selected from the group consisting of: H and C_{1-3}alkyl;

wherein R^{12} is H, or C_{1-3}alkyl; and

wherein the stereochemistry of the double bond denoted "*" is entgegen or zusammen.

2. The compound of Claim 1, wherein W is O, D is O, G is C, n is 1, p is 0, and R^2, R^3, R^7, R^8, R^9, R^{10}, and R^{12} are H.

3. The compound of Claim 2, wherein X is a C_{1-3}alkylene, and V is a phenylene, naphthalenylene, or a 9- to 12-membered bicyclic arylene.

4. The compound of Claim 2, wherein X is a C_{1-3}alkylene, and V is a 5-membered heteroarylene, a 6-membered heteroarylene, or an 8- to 12-membered bicyclic heteroarylene.

5. The compound of Claim 4, wherein V is selected from the group consisting of a 2-thienylene, a 3-thienylene, a 2-furanylene, a 3-furanylene, a pyrimidinylene and a pyridinylene.

6. The compound of Claim 2, wherein A is absent, B is a C_{1-3}alkylene, wherein L is a 5-membered heteroaryl, a 6-membered heteroaryl, an 8- to 12-membered bicyclic heteroaryl, a phenyl, a naphthalenyl or a 9- to 12-membered bicyclic aryl.

7. The compound of Claim 6, wherein B is a C_{1-3}alkylene and L is a phenyl.

8. The compound of Claim 2, wherein K is S, Y is C(O), and R^6 is H.

9. The compound of Claim 2, wherein K is S, Y is C(S), and R^6 is H.

10. The compound of Claim 2, wherein K is NH, Y is C(O) and R^6 is H.

11. The compound of Claim 2, wherein said compound is selected from the group consisting of:

4-(4-tert-Butyl-benzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one;

5-[4-(2,6-Di-tert-butyl-pyridin-4-ylmethyl)-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-6-ylmethylene]-thiazolidine-2,4-dione;

6-(Oxo-2-thioxo-thiazolidin-5-ylidenmethyl)-4-[2-(4-trifluoromethyl-phenyl)-ethyl]-4H-benzo[1,4]oxazin-3-one;

4-(4-Methanesulfonyl-benzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one;

4-(3-tert-Butyl-5-hydroxymethyl-benzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one;

5-[4-(3,5-Di-tert-butyl-4-hydroxy-benzyl)-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-6-ylmethylene]-thiazolidine-2,4-dione;

5-{4-[4-(4-Methyl-piperazin-1-ylmethyl)-benzyl]-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-6-ylmethylene}-thiazolidine-2,4-dione;

4-Cyclohexylmethyl-6-(4-oxo-2-thioxo-oxazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one;

4-[3-tert-Butyl-5-(morpholine-4-carbonyl)-benzyl]-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-1,4-benzoxazin-3-one;

5-[1-[4-(3-tert-Butyl-5-morpholin-4-ylmethyl-benzyl)-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl]-meth-(Z)-ylidene]-thiazolidine-2,4-dione;

4-(3,5-Difluoro-4-hydroxy-benzyl)-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-benzo[1,4]oxazin-3-one;

5-[4-(3-Chloro-4-fluoro-benzyl)-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-ylmethylene]-thiazolidine-2,4-dione; and

4-(1-tert-Butyl-5-methyl-1H-pyrazol-3-ylmethyl)-6-(4-oxo-2-hioxo-thiazolidin-5-ylidenemethyl)-4H-benzo[1,4]oxazin-3-one.

12. The compound of Claim 1, wherein W is S, D is O, G is C, n is 1, p is 0, and R^2, R^3, R^7, R^8, R^9, R^{10}, and R^{12} are H.

13. The compound of Claim 1, wherein W is N, R^{21} is methyl, D is O, G is C, n is 1, p is 0, and R^2, R^3, R^7, R^8, R^9, R^{10}, and R^{12} are H.

14. The compound of Claim 1, wherein W is O, D is O, G is N, n is 1, p is 0, and R^2, R^3, R^7, R^8, R^9, R^{10}, and R^{12} are H.

15. The compound of Claim 1, wherein W is O, D is O, G is C, n is 1, p is 0, R^{10} is methoxy, and R^2, R^3, R^7, R^8, R^9, and R^{12} are H.

16. The compound of Claim 1, wherein W is O, D is O, G is C, n is 1, p is 0, R^{10} is methyl, and R^2, R^3, R^7, R^8, R^9, and R^{12} are H.

17. The compound of Claim 1, wherein W is O, D is O, G is C, n is 1, p is 0, R^7 and R^{10} are methyl, and R^2, R^3, R^8, R^9, and R^{12} are H.

18. The compound of Claim 2, wherein W is O, D is O, G is C, n is 1, p is 0, R^{10} is chloro, and R^2, R^3, R^7, R^8, R^9, and R^{12} are H.

19. The compound of Claim 1, wherein W is O, D is O, G is C, n is 1, p is 0, R^{10} is fluoro, and R^2, R^3, R^7, R^8, R^9, and R^{12} are H.

20. The compound of Claim 19, wherein said compound is selected from the group consisting of:

4-(3-Methanesulfonyl-benzyl)-6-[4-oxo-2-thioxo-thiazolidin-(5Z)-ylidenemethyl]-4H-benzo[1,4]oxazin-3-one;

5-[1-{4-[3-tert-Butyl-5-(1-hydroxy-1-methyl-ethyl)-benzyl]-8-fluoro-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl}-meth-(Z)-ylidene]-thiazolidine-2,4-dione;

8-Fluoro-4-[4-(1-hydroxy-1-methyl-ethyl)-benzyl]-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-benzo[1,4]oxazin-3-one;

5-[8-Fluoro-4-(4-fluoro-benzyl)-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-ylmethylene]-thiazolidine-2,4-dione;

4-(3-Chloro-4-fluoro-benzyl)-8-fluoro-6-(4-oxo-2-thioxo-oxazolidin-5-ylidenemethyl)-4H-benzo[1,4]oxazin-3-one;

8-Fluoro-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4-quinolin-6-ylmethyl-4H-1,4-benzoxazin-3-one; and

4-(3,4-Dichloro-benzyl)-8-fluoro-6-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-4H-benzo[1,4]oxazin-3-one.

21. The compound of Claim 1, wherein W is O, D is O, G is C, n is 1, p is 0, R^2 is methyl, and R^3, R^7, R^8, R^9, R^{10}, and R^{12} are H.

22. The compound of Claim 1, wherein W is O, D is O, G is C, n is 0, p is 0, and R^2, R^3, R^7, R^9, R^{10}, and R^{12} are H.

23. A method of treating a subject suffering from a PI3K-mediated disorder or condition comprising: administering, to a subject suffering from a PI3K-mediated condition or disorder, a pharmaceutical composition comprising a therapeutically effective amount of a compound of Claim 1 and a pharmaceutically acceptable carrier.

24. The method of Claim 23, wherein said PI3K-mediated condition or disorder is selected from the group consisting of:
rheumatoid arthritis, osteoarthritis, inflammatory diseases, and autoimmune diseases.

25. The method of Claim 23, wherein said PI3K-mediated condition or disorder is selected from the group consisting of:
cardiovascular diseases, atherosclerosis, hypertension, deep venous thrombosis, stroke, myocardial infarction, unstable angina, thromboembolism, pulmonary embolism, thrombolytic diseases, acute

arterial ischemia, peripheral thrombotic occlusions, and coronary artery disease.

26. The method of Claim 23, wherein said PI3K-mediated condition or disorder is selected from the group consisting of:
cancer, breast cancer, gliobastoma, endometrial carcinoma, heptocellular carcinoma, colon cancer, lung cancer, melanoma, renal cell carcinoma, thyroid carcinoma, small cell lung cancer, squamous cell lung carcinoma, glioma, breast cancer, prostate cancer, ovarian cancer, cervical cancer, leukemia, cell lymphoma, and lymphoproliferative disorders.

27. The method of Claim 23, wherein said PI3K-mediated condition or disorder is selected from the group consisting of:
type II diabetes.

28. The method of Claim 23, wherein said PI3K-mediated condition or disorder is selected from the group consisting of:
respiratory diseases, bronchitis, asthma, and chronic obstructive pulmonary disease.

29. The method of Claim 23, wherein said compound is a compound of any one of Claims 1-22.

30. A pharmaceutical composition comprising:
a therapeutically effective amount of a compound of Claim 1 and a pharmaceutically acceptable carrier.

31. A pharmaceutical composition comprising:
a therapeutically effective amount of a compound of any one of Claims 1-22 and a pharmaceutically acceptable carrier.